REMARKS

Applicant respectfully requests reconsideration.

Claims 62-69 were previously pending in this application.

By this amendment, Applicant is amending claim 62 without prejudice or disclaimer. As a result, claims 62-69 are now pending with claims 62-63 and 66-69 corresponding to the elected species currently under examination.

Basis for this amendment can be found throughout the specification including, for example, page 44, line 24, through page 46, line 12. No new matter has been added.

Rejections under 35 U.S.C. §112

Pages 3 and 5 of the Office Action both indicate that claims 62-63 and 66-69 were rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the enablement requirement. However, the detailed rejections on pages 3-4 of the Office Action appear to relate to written description whereas the detailed rejections on pages 5-10 of the Office Action relate to enablement. Accordingly, the following paragraphs address written description and enablement separately.

Written description:

The Examiner alleges on pages 3-4 of the Office Action that Applicant was not in possession of the invention. Applicant respectfully disagrees and points at least to the passages on page 44, line 24, through page 46, line 12 for written description support of the claims as amended. For example, lines 1-7 of page 46 provide a detailed description of Applicant's invention as presently claimed:

> Although applicants are not bound by the mechanism, it is believed that the ability of the immunostimulatory nucleic acids to prevent the development of resistant strains results from the ability of the nucleic acids to induce an immune response leading to an improved response by the immune system against a microorganism. At the same time, the anti-microbial agent is

> functioning to kill or inhibit the microorganism. This dual action may result in rapid inhibition of the invading microorganism, reducing the time in which genetic modifications can occur prior to cell death or inhibition.

This aspect of the invention is also explained at least on lines 6-14 of page 7, where the specification describes the advantage of combining agents that use different mechanisms for attacking microbial infections:

> The immunostimulatory nucleic acids when combined with the anti-microbial agents have many advantages over the use of each composition alone for the treatment of infectious disease. The immunostimulatory nucleic acids function in some aspects by simultaneously inducing innate and antigen specific immune responses leading to a multifaceted attack by the immune system on the microorganism. The anti-microbial agents specifically attack the microorganism, causing death or inhibition of the microorganism. The immunostimulatory nucleic acids provide long-lasting effects, thus reducing dosing regimes, improving compliance and maintenance therapy, reducing emergency situations; and improving quality of life.

Applicant also provides a detailed description of different types of immunostimulatory nucleic acids and specific examples of immunostimulatory nucleic acids (see, for example, line 26 on page 7 through line 27 on page 18) that can be used to treat a microbial infection via an immunostimulatory mechanism in contrast to an antibiotic that directly attacks the microorganism responsible for the microbial infection. In addition, Applicant provides a detailed description of different types of antibiotics and specific examples of antibiotics (see, for example, line 16 on page 26 through Table 2 on page 34) that can be used to treat a microbial infection.

The Examiner pointed to publications by Krieg et al. and Mutwiri et al. to support the proposition that Applicant was not in possession of the invention. Applicant respectfully disagrees with the Examiner's position and submits that these publications fail to negate Applicant's detailed

explanation of the invention and detailed description of the structures and functions of the immunostimulatory nucleic acids and antibiotic agents that can be used together to prevent the development of antibiotic resistant microbial infections. The observation that certain immunostimulatory oligonucleotides have different levels of activity does not undermine the claimed invention in the same way that different levels of activity observed for different antibiotics do not undermine the claimed invention. Indeed, Applicant refers throughout the specification to different factors that should be considered when selecting immunostimulatory nucleic acids and antibiotics.

Therefore, Applicant submits that the application complies with the written description requirement and respectfully requests that this rejection be reconsidered and withdrawn.

Enablement:

The Examiner alleges on pages 5-10 of the Office Action that the invention was not enabled. Applicant respectfully disagrees and submits that the amended claims recite features that are described in such a way that one or ordinary skill in the art would be able to practice the invention without undue experimentation.

The claims as amended recite administering to a subject prior to, at the same time as or after the subject has received antibiotic therapy against a microbial infection an effective amount of an immunostimulatory nucleic acid for promoting an immune response against the microbial infection, thereby preventing the development of an antibiotic resistant microbial infection. Applicant respectfully submits that one of ordinary skill in the art can identify or administer an antibiotic against a microbial infection as described in the specification. Applicant further submits that one of ordinary skill in the art can administer an immunostimulatory nucleic acid as claimed based on the teachings of the specification. As described above, the specification provides a detailed description of antibiotics, immunostimulatory nucleic acids, and methods for administering them to prevent the development of antibiotic resistant microbial infections.

On pages 5-10 of the Office Action, the Examiner provided a number of collateral lines of evidence based on the alleged state of the art to support the position that "the state of the art is unpredictable with regard to preventing antibiotic resistance" and thus the instant claims are not

enabled. Applicant respectfully submits that the Examiner's interpretation as presented in the Office action is inconsistent with case law, in view of which Applicant presents arguments below.

The Examiner cited Krieg et al. for the proposition that "each immunostimulatory nucleic acid must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies." The Examiner cited Mutwiri et al. for the proposition that "the immunostimulatory activity of oligonucleotides containing the CpG is very species specific." The Examiner stated that "Yamamoto et al. reports that oligonucleotides containing the CpG motif failed to improve the survival in mice challenged with influenza." The Examiner also cited Gura for the proposition that "synthetic oligonucleotides have caused side effects in experimental animals." Applicant does not agree with the conclusions drawn by the Examiner. However, taken on their face, the cited references point out certain variations in responses to immunostimulatory CpG oligonucleotides. However, Applicant submits that these variations do not negate the claimed invention. Applicant respectfully disagrees with the implied notion that such variations amount to unpredictability or undue experimentation. Variations associated with therapeutics amongst species, or in some cases amongst individuals of the same species, are to be expected. Like any therapeutic reagent, therefore, it is reasonably expected that optimal effects of the immunostimulatory oligonucleotides of the instant invention can depend on various factors, as noted by the Examiner, such as various modes of administration. Applicant does not dispute the notion. In fact, even with an FDA-approved drug, a certain degree of optimization is required. That in itself, however, does not render the claimed invention unpatentable. Chapter 2100 of the MPEP states, "An applicant's specification must enable a person skilled in the art to make and use the claimed invention without undue experimentation. The fact that experimentation is complex, however, will not make it undue if a person of skill in the art typically engages in such complex experimentation." Given the amount of information provided regarding CpG nucleic acids and the antibiotic agents, the skilled artisan would have no trouble implementing the invention as claimed. That is, the skilled artisan would know how to make and prepare a composition comprising an immunostimulatory nucleic acid as described in the specification and administering it to a subject in addition to an antibiotic. In addition, the skilled artisan would know how to optimize the same, based on the various parameters as presented in the detailed description.

Applicant further wishes to note that case law is clear in that issues such as optimization and safety of a therapeutic agent are to be properly left to the FDA (See *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA]."). In the instant case, Applicant provided a detailed explanation and description of the invention, and the evidence as a whole should teach one skilled in the art how to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 USPQ 286, 294 (CCPA 1973). The evidence provided by applicant need not be *conclusive* but merely *convincing* to one skilled in the art.

Thus, what is being alleged by the Examiner as "unpredictable" is not the immunostimulatory property of the claimed invention *per se*, but with respect to the aspect of optimization and safety, e.g., the degree of efficacy, optimal administration mode, etc., which, again, relates to a regulatory issue that falls within a territory of the Food and Drug Administration, not to the statutory standards of patentability as set forth in 35 U.S.C. In fact, one cannot possibly determine the parameters of safety without a controlled clinical trial, and it is well established that a clinical trial is not required for enablement.

Finally, the Examiner stated that "the art teaches that there is a struggle to control infectious diseases and the immunostimulatory and immunosuppressive agents are capable of enhancing host defense mechanisms to provide protection against infection" and the Examiner cited Masihi and BonHoefer. Respectfully, and without acquiescing to the Examiner's characterization of these references, Applicant submits that this statement by the Examiner does not address the enablement of the invention, but rather indicates that there is a need in the art to control infectious diseases.

In conclusion, a number of references were cited in the office action. However, it is unclear to Applicant as to how each of the cited references supports the Examiner's position that the instantly claimed invention lacks enablement. In particular, Applicant notes that the cited references do not necessarily contradict the essence of the present invention.

The Examiner also stated that "the specification does not contain any working examples that are directed to the claimed invention" and argued that the specification "does not provide any evidence that the claimed method would function in vivo or in vitro." Finally, the Examiner concluded that "it would require undue experimentation for one skilled in the art to use the claimed

methods." Applicant respectfully disagrees and contends that a sufficiently detailed description and explanation of the claimed methods of the invention, including the immunostimulatory nucleic acids, the antibiotics, and methods for their administration and evaluation to prevent the development of antibiotic resistant microbial infections is disclosed and thus the full scope of the instant claims is enabled.

The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). In *Wands* the court observed that "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed . . . ." Id. Contrary to the Examiner's assertion that there is a "lack of guidance," Applicant respectfully contends that adequate guidance is provided to the direction in which the experimentation should proceed such that those skilled in the art can use the claimed invention for preventing the development of antibiotic resistant microbial infections.

Therefore, Applicant submits that the application complies with the enablement requirement and respectfully requests that this rejection be reconsidered and withdrawn.

Accordingly, reconsideration and withdrawal of all the rejections under 35 U.S.C. §112, first paragraph, is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: February 25, 2008

Respectfully submitted,

By Pat R H Wal

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